

## O.R. Applications

Living with influenza: Impacts of government imposed  
and voluntarily selected interventionsKarima R. Nigmatulina<sup>a</sup>, Richard C. Larson<sup>b,\*</sup><sup>a</sup> Operations Research Center, Massachusetts Institute of Technology, Cambridge, MA 02139, USA<sup>b</sup> Engineering Systems and Civil and Environmental Engineering, Massachusetts Institute of Technology, Cambridge, MA 02139, USA

Received 8 October 2007; accepted 14 February 2008

Available online 21 February 2008

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**Abstract**

Focusing on mitigation strategies for global pandemic influenza, we use elementary mathematical models to evaluate the implementation and timing of non-pharmaceutical intervention strategies such as travel restrictions, social distancing and improved hygiene. A spreadsheet model of infection spread between several linked heterogeneous communities is based on analytical calculations and Monte Carlo simulations. Since human behavior will likely change during the course of a pandemic, thereby altering the dynamics of the disease, we incorporate a feedback parameter into our model to reflect altered behavior. Our results indicate that while a flu pandemic could be devastating; there are coping methods that when implemented quickly and correctly can significantly mitigate the severity of a global outbreak. © 2008 Elsevier B.V. All rights reserved.

**Keywords:** Stochastic modeling; Pandemic flu; OR in health services; Heterogeneity; Behavior

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**1. Introduction**

Influenza pandemics have occurred intermittently over centuries killing millions of people worldwide. When a novel influenza virus emerges from the animal or avian reservoir humans do not have immunity to this new strain and everyone is susceptible. While medical advances over the past century have been significant, it still takes four to six months, sometimes more, to develop and produce sufficient vaccine. If a new flu virus emerges, it can spread quickly throughout the world causing a pandemic. Such a disaster would not only place extraordinary and sustained demands on the public health and medical care systems, but will also burden the providers of essential services and strain the operations of all businesses. The federal government forecasts that up to 40% of the US population may be absent from their daily routines for extended periods as a result of illness or care-giving responsibilities (IPNSPI, 2006). High rates of worker absenteeism could in turn affect critical infrastructure, including the operations of water treatment facilities and power plants, while efforts to slow the spread of disease could limit the availability of food. A pandemic would impact all sectors of society.

The US National Intelligence Council's 2020 Project "Mapping the Global Future" identified a flu pandemic as the single most important threat to the global economy (Karesh and Cook, 2005). A report from the Lowy Institute for International Policy concluded that even a very mild pandemic, like the 1968–1969 version, would result in a global economic loss of \$330 billion and a human loss of 1.4 million (McKibbin, 2006). A catastrophically severe 1918 version is forecasted to wipe out \$4.4 trillion of global economic output and kill more than 140 million people (McKibbin, 2006). The potential number of deaths is greater than those forecasted from a nuclear exchange between two warring nations.

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\* Corresponding author. Tel.: +1 617 253 3604; fax: +1 617 252 1566.

E-mail address: [rclarson@mit.edu](mailto:rclarson@mit.edu) (R.C. Larson).

The current most discussed pandemic threat is caused by the H5N1 strain of the Influenza A virus which has resulted in an outbreak of avian influenza in Asia, Africa and Europe. The virus has infected birds in over 35 countries and has resulted in the deaths, through illness and culling, of over 200 million birds across Asia. Various control measures have been attempted, but the virus persists and is endemic in Southeast Asia, found in long-range migratory birds, and is unlikely to be eradicated soon. The H5N1 virus is able to infect a wide range of hosts, and as of August 31st 2007 has been reported to have infected 327 people in 12 countries, resulting in 199 deaths (WHO, 2008). While this virus has not shown an ability to transmit efficiently between humans, there is concern that it will acquire this capability through genetic mutation or exchange of genetic material with a human influenza virus. Even if the currently circulating H5N1 virus does not result in the next human pandemic, evidence suggests that a different influenza strain is likely to emerge and cause the next catastrophic pandemic. For example, H9N2 infected children in China in 1999 and 2003; H7N2 caused infections in New York and Virginia in 2002 and 2003; and H7N3 infected poultry workers in Canada in 2004 (CDC, 2005). In 2003 H7N7 infected more than 1000 people in the Netherlands, even passing from human to human (Enserink, 2004). Overall, the National Academy of Sciences, CDC and chief medical personnel across the world agree that an influenza pandemic is only a matter of time (Gerberding, 2005; Carr-Brown, 2005; Knox, 2005).

The potential magnitude of this disaster requires advance planning, early preparedness and rapid action after detection of efficient transmission of a new and lethal virus. During the past few years policymakers have begun to realize the severity of this threat, and preparedness plans have started to develop across many layers of government. The US Department of Health and Human Services issued guidelines in November 2005, but left it to the states to produce specific plans, indicating that states should not rely on the federal government for much help during a pandemic. States have released versions of their pandemic plans, but most states do not include personal contact-avoidance or other more non-pharmacologic containment steps (Holmberg et al., 2006). One authority was even quoted saying that “short of obtaining [antiviral] drugs, there is not much we can do to prepare” for a pandemic (Weaver, 2005). To explain this omission, policymakers point to the lack of epidemiologic data proving the effectiveness of non-pharmaceutical interventions. However, evidence from the SARS outbreak indicate that improved hygiene, masks and other behavioral changes decreased the spread of respiratory disease by 90% (Lo Janice et al., 2005)! Modeling these disease spread processes helps us understand the potential effect of interventions before the flu hits. The goal is to help provide decision makers with a systematic approach to evaluating and comparing the effectiveness of various government imposed containment strategies and voluntary behavioral changes.

In this paper, we review the implications and then build on Larson’s model (Larson, 2007) to consider the spread of infection between several loosely linked communities. After adding this spatial structure, we discuss the effectiveness of more complex and realistic control strategies and consider the consequences of reactive behavioral changes. The analysis of imposed interventions includes the evaluation of travel restrictions in stopping the spread of the virus. Since people are likely to alter their daily behavior based on the information they receive, we propose a unique approach to incorporating human reaction into our model. After examining each of these factors individually we compare and consider their combined potential in decreasing the extent of the outbreak. Our results indicate that with proper planning, even without any vaccines or anti-virals, we can make a difference in the course of the next pandemic.

## 2. Background

### 2.1. Literature review

The types of models that have been used to describe the spread of infection range from basic differential equations models to detailed stochastic agent-based simulations. One of the most widely used approaches relies on one specific parameter for the description of infection spread – the basic reproductive number  $R_0$ : the average number of infections a typical infectious individual will generate in a fully susceptible population (Diekmann et al., 1990). An infection can grow in a fully susceptible population if and only if  $R_0 > 1$  (Hethcote, 2000). As the population of susceptibles is depleted the generation specific reproduction number,  $R(t)$  reflects how many secondary infections will result from each newly infected individual on generation  $t$ . There are three types of approaches based on the basic reproduction number: models that express  $R_0$  in terms of parameters that describe the virus’ virulence and morbidity (MacDonald, 1952, Hyman and Li, 2000), models that fit the  $R_0$  parameter to data using branching or martingale models (Becker, 1974, 1989) and models that use endemic equilibrium data to derive  $R_0$  (Dietz and Heesterbeek, 2002, Dietz, 1975). While using  $R(t)$  or  $R_0$  provides a computationally intuitive basis for describing disease dynamics, this approach neglects important heterogeneity and stochasticity complexities (Eubank et al., 2004, Larson, 2007). Unfortunately, while  $R_0$  has some benefits, it has often been a limiting modeling approach that many adhere to without question.

Many recent models incorporate information about social network structures in order to understand the impact of social mixing patterns. Network models can range from simple lattice and random mixing networks, to small-world graphs or incredibly detailed social networks where nodes represent people, and edges represent specified relationships or

interactions. These networks provide a backbone for stochastic Monte Carlo models that simulate how an infection could spread from one source node to the rest of the population. These studies have shown that the degree, betweenness and farness of nodes alter disease dynamics (Christley et al., 2005).

There are also stylized models of more realistic social networks such as the Glass et al. model. In their work all persons within each household were linked to each other with mean link contact frequencies of 6/day. Every person also belonged to 1 multiage extended family group with a mean link contact frequency of 1/day. Furthermore, mean link contact frequencies for children in a school are 6/day. Teenager classes, adult work, and gatherings of older adults result in 1 mean link contact per day. By incorporating these more realistic nuances the group found the importance of children mixing schools as a key driver of infection. Their dramatic finding was that children and teenagers who compose only 29% of the population are responsible for 59% of infection. This group did not rely on  $R_0$ , in fact they point out that the calculation of  $R_0$  from small-community data such as theirs is ambiguous.

A significant portion of current research has taken this even further making use of the advancement of computer capabilities. For example, Los Alamos with the use of their supercomputer, initially created for nuclear weapons' study, models every individual within the US and study flu spread (Germann et al., 2006). Using census data and transportation information they produced a complex program which simulated, at a very detailed level, the interaction of over 240 million "people" over 180 days. The modelers openly acknowledge that "the spontaneous public response to news of an approaching pandemic will affect social behavior in unpredictable ways". To reflect that in their simulation they implement various social distancing behaviors that are expected given an initial pandemic curve. The problem is that human reaction should reflect the updated epidemic, but this dynamic concept is not incorporated. As a result the social intervention strategies are terminated too early to be fully effective. The researchers' conclusions are that vaccines and antiviral drugs will be the salvation to the pandemic disaster; however, limiting contact between people through travel restrictions, quarantine and school closing will only buy time, perhaps enough time for vaccine production, but will not stop the epidemic.

Two other recently developed agent-based models attempt to predict the scenario that could occur in Southeast Asia where the disease is expected to commence. Ferguson et al. conclude that as long as the virus was less transmissible than the 1918 flu, combining geographically and socially targeted prophylaxis and social distancing could stop a nascent pandemic (Ferguson et al., 2003). Similar in intention, the Longini et al. group has similar findings (Longini et al., 2005). Both works highlight the importance of early diagnosis and immediate treatment, the significance of proper timing is a shared finding that should sway policy makers' flu containment measures. Yet again these models do not attempt to model reactive human behavior changes because it is too unpredictable.

## 2.2. Model basics

In order to capture the complexities of a heterogeneous population, we follow Larson's approach and divide the population of each community into several groups based on their daily social activity levels. We will assume that face-to-face social contacts within each community will occur as a homogenous Poisson process with rate parameters dependant on the level of social activity. For the rest of the numerical calculations and simulations we split the population of each community into three groups: high, medium and low activity persons. We define

- $\lambda_H^A$  = average number of social contacts of a High activity person in Community A/day
- $\lambda_M^A$  = average number of social contacts of a Medium activity person in Community A/day
- $\lambda_L^A$  = average number of social contacts of a Low activity person in Community A/day
- $n_H^A$  = initial total population of High activity persons in Community A
- $n_H^{I^A}(t)$  = number of High activity infective & asymptomatic persons in Community A on day  $t$
- $n_H^{S^A}(t)$  = number of High activity susceptible persons in Community A on day  $t$ <sup>1</sup>

Let us clarify that throughout our work we define one day as one generation of the infectious period of the virus. One day in our model is closer to 2–3 actual days.

We initiate the outbreak with one infectious individual who spreads the disease during day 0. By the end of this day the initial seeder self-isolates, recovers or dies, and only the newly infected individuals spread the virus on day one. Evidence of self-isolating behavior has been observed in practice (Zeng and Wagner, 2002) and reflects peoples' departure from the infectious category. An infected individual never reenters the susceptible population since people gain immunity if they survive the disease. This pattern continues for the rest of the outbreak.

From Larson's paper we know that for a random person on day  $t$  in Community A the probability that the next interaction will be with an infected individual is

<sup>1</sup> The remaining variables for each of the activity groups are defined according to the above established pattern.

$$\beta^A(t) \equiv \frac{\lambda_H^A n_H^I{}^A(t) + \lambda_M^A n_M^I{}^A(t) + \lambda_L^A n_L^I{}^A(t)}{\lambda_H^A n_H^A + \lambda_M^A n_M^A + \lambda_L^A n_L^A}.$$

Given all the  $\lambda$ 's and assuming homogeneous susceptibility

$p$  = probability that a susceptible person become infected, given contact with an infectious individual.

We know that the probability that a random susceptible High activity person in Community A gets infected on day  $t$  is

$$p_H^{S\ A}(t) = 1 - e^{-\lambda_H^A \beta^A(t) p}.$$

In Table 1, we present the base case parameter values that we continue to use throughout this paper to present the results of our modeling analysis based on the above formulations.

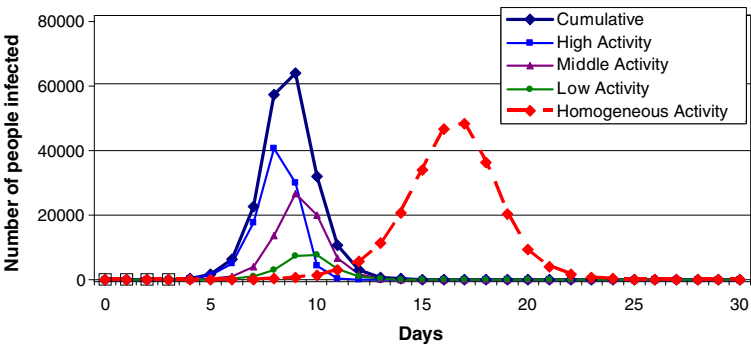
Graph 1 is an illustration of average infection spread within a hypothetical community; notice that the virus spreads faster through a population with several activity levels when compared to a homogeneous community with an equivalent overall average activity level. The imprecise, but widely accepted, definition of  $R_0$  is the average number of people infected by the initial seeder in a fully susceptible population. For the heterogeneous and uniform communities, the expected number of daily contacts of a randomly selected person from either population will be the same, thus using one interpretation, without knowledge of the intra activity group interactions,  $R_0$  is identical in both instances. Graph 1 illustrates a fundamental flaw in the usage of only one averaging parameter such as  $R_0$  (or  $R(t)$ ) as the sole modeling factor.

Diversity of human activity levels is not the only heterogeneity that differentiates individuals; we can also include heterogeneity of people's susceptibility to infection. We can split the population into groups based on their vulnerability to the disease; in this case we define different probabilities of transmission given contact with an infected individual. For the sake of fair comparison we ensure that on average susceptibility – the probability of infection given contact – is identical in the

Table 1  
Parameters used as the base case for the research<sup>a</sup>

Parameter name	Variable	Community A
Population of High activity level	$n_H^A$	100,000
Population of Medium activity level	$n_M^A$	100,000
Population of Low activity level	$n_L^A$	100,000
Social contacts of High activity persons	$\lambda_H^A$	50
Social contacts of Medium activity persons	$\lambda_M^A$	10
Social contacts of Low activity persons	$\lambda_L^A$	2
Conditional probability of successful transmission	$p$	.10
Travelers from A to B of High activity	$T_{AB}^H$	2
Travelers from A to B of Medium activity	$T_{AB}^M$	2
Travelers from A to B of Low activity	$T_{AB}^L$	2
Travelers from B to A of High activity	$T_{BA}^H$	2
Travelers from B to A of Medium activity	$T_{BA}^M$	2
Travelers from B to A of Low activity	$T_{BA}^L$	2

<sup>a</sup> We use the Wallinga paper as a base for our average number of daily contacts (Wallinga et al., 2006; Fu, 2005, 2007).



Graph 1. Comparing spread of infection between heterogeneously and uniformly active communities of 300,000 individuals.

uniform and diverse populations. We find that again the diverse groups have a higher and earlier epidemiological peak, and potentially fewer total infections since the disease can die out faster. Relying singly on  $R_0$  would not have captured the possibility of these significantly different outcomes.  $R_0$  is meaningless and often misleading without knowledge of the societal structure and immunal propensity to the flu of the underlying population. A central observation from [Graph 1](#) is that the immunally weak and socially active individuals are not only themselves more predisposed to the flu, but are also the key spreaders of infection to the other groups.<sup>2</sup>

### 3. Spatial spread: Multi-community models

Historical examples show that one infected traveler is enough to infect a whole population. During the 1918–1919 flu many Alaskan villages were completely devastated by influenza because the man who brought the villagers their mail also brought the flu ([Underwood, 2005](#)). In China's remote Shanxi province, the spread of the 1918 pandemic was traced to a single woodcutter, tramping from village to village ([Greger, 2006](#)). In Canada, the virus wore the uniform of a stubborn Canadian Pacific Railways official who flouted quarantine, dropping off infected repatriate soldiers from Quebec all the way west to Vancouver ([Greger, 2006](#)). The only places to escape unscathed during the 1918 pandemic were three small islands completely shut off from the outside refusing even mail delivery ([Herda, 1995](#)). On mainland one successful resort town in New Zealand went to the extreme of cutting itself off from the world using a “rotating roster of shotgun-wielding vigilants” ([Greger, 2006](#)).

There are more recent examples of one traveler sparking a large outbreak; a pilgrim returning from Mecca was the source of a large smallpox outbreak in Yugoslavia in the early 1970s that resulted in 174 Yugoslav cases and 35 deaths ([WHO, 1972](#)). The pilgrim contracted the infection in Baghdad while visiting a religious site, but because his symptoms were mild, he was never confined to bed and was able to continue his travels, return home and start an outbreak. Finally, in the case of SARS, studies indicate that thermal screening and health declarations of travelers did not significantly stop the flow of determined travelers or the spread of SARS ([Bell, 2004](#)). These examples indicate the importance of a model that captures geographical dispersion of infection resulting from very few traveling infected people.

#### 3.1. Fully connected communities model

##### 3.1.1. Two communities model

The first layer of realism that we added to Larson's model is spatial complexity: we developed a loosely connected multi-community structure using Monte Carlo simulation to model disease spread between cities. In a two community model each community has its own demographic and epidemiological composition. The populations are loosely connected by very few random daily travelers. A certain number of randomly selected people from each activity level  $j$ ,  $T_{AB}^j$ , travel overnight from A to stay exactly one day in B before returning home the next night. In the base case  $T_{AB}^j = T_{BA}^j = 2$ , giving us a total of 12 travelers going back and forth between two communities. During a visitor's one-day stay in the adjacent community his interaction level is unchanged from what it was within his/her home community.

We initiate the outbreak with an infectious seed in Community A, and the disease propagates to other individuals within this community ([Graph 1](#)). Since travelers continue their movement between communities, eventually it is likely that one of the travelers becomes infected, thus he becomes the passageway for the transition of the infection from one community to another. Let us emphasize that there are two ways that Community B can get the infection.

1. An infected individual residing in A travels from A to B and infects people in Community B which instigates the outbreak in B (even though the traveler returns to A at the end of the day).
2. A susceptible individual residing in B travels from B to A and gets infected while visiting Community A. The newly infected individual returns home to Community B and becomes the initial spreader within his community.

We have two processes competing to bring the pandemic to Community B. After the pandemic is in both populations, we assume that the few individuals traveling back and forth, with or without the infection, will not change the disease dynamics in either of the communities.

This structure allows us to apply large population-based averaging techniques to model the occurrences within the community. At the same time, we use Monte Carlo simulation to model the stochastic person-to-person transmission of infection to reflect the intra-community spread of infection. Using this structure, we address the question: if the initial case occurs on day 0 within Community A, on average how quickly will it spread to an adjacent community?

<sup>2</sup> These qualitative results are supported by findings of the real-time surveillance system at Boston's Children's Hospital which found children, who, compared to adults, have more contacts and increased vulnerability, to be the drivers of seasonal flu; in particular, preschoolers are considered to be “hotbeds of infection” ([Neergaard, 2005](#)).



The probability of the virus spreading to a new community changes on a daily basis. In order to find the probability that on day  $i$  at least one infectious individual from activity level  $j$  visits Community B, we can “identify” this random individual and find the probability that this traveler gets infected during day  $i - 1$ . The probability that exactly  $k$  infected individuals of activity level  $j$  travel from A to B and bring in the virus on day  $i$  is

$$p_j^{AB}(k, t) = \binom{T_{AB}^j}{k} (1 - e^{-\lambda_j^A \beta^A (t-1)p})^k (e^{-\lambda_j^A \beta^A (t-1)p})^{T_{AB}^j - k}.$$

Thus the probability that none of day  $i$ 's travelers from A to B are infectious is

$$\prod_j p_j^{AB}(0, t) = \prod_j (e^{-\lambda_j^A \beta^A (t-1)p})^{T_{AB}^j}.$$

Symmetrically, the probability that a traveler from Community B gets infected and brings back home the infection on day  $i$  is the same. So  $p_j^{AB}(k, t) = p_j^{BA}(k, t)$ . Lastly the probability of having the infection enter for the first time on day  $i$  is

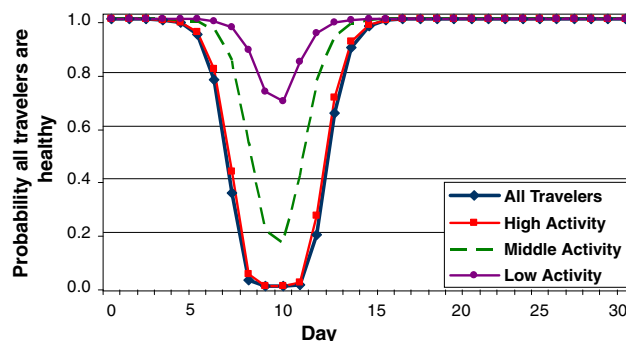
$$P(i \text{ is the 1st day of infection in B}) = \prod_{t=0}^{i-1} \prod_j p_j^{AB}(0, t) p_j^{BA}(0, t) (1 - p_j^{AB}(0, i) p_j^{BA}(0, i)).$$

Notice that the probability of never infecting a neighboring community is greater than 0, thus the expected time till the next community gets contaminated is infinity. As a result we cannot rely on expected value, instead it is helpful to know the probability that day  $t$  is the first day of infection entering into the neighboring community. From Graph 2 we see the probability of infection spread is almost certain if the 12 travelers maintain their trips and if the virus is relatively transmissible amongst individuals.

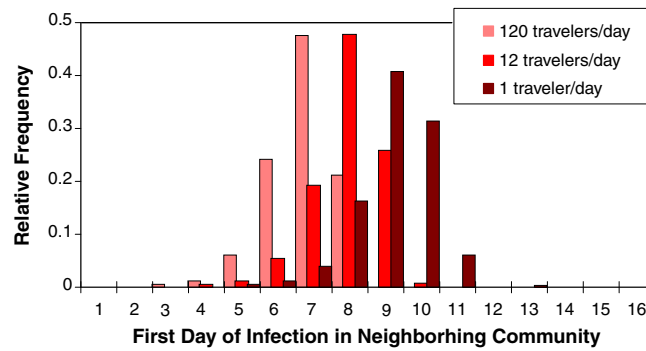
Performing sensitivity analysis on the transmissibility parameter we find that if  $p$  is low enough, not only will the infection die out quickly within Community A, but the probability of spreading to Community B also decreases. One approach is to use the often referred to fact that infection dies out at  $R_0 < 1$  and apply it to calculate the tipping point. To evaluate  $R_0$  we can consider the number of daily contacts multiplied by the probability that one such contact will lead to transmission and then averaged over the whole population. Assuming that the population is large enough and that each interaction outcome is independent of the others  $R_0$  can be simplified to the population's average number of daily contacts multiplied by the average probability of transmission per contact. Then in the community on average there will be  $(50 + 10 + 2)/3 = 20.67$  daily contacts, so this implies that a  $p < 0.0484$  should stop the pandemic. When we use our heterogeneous community model we find that the epidemic will be stopped when the probability of transmission is decreased to below  $p < 0.03$ , which is significantly different. As long as the virus does not achieve epidemic status within the initial community, it is not likely to transfer to neighboring towns, but the highly active members of heterogeneous communities make the infection more persistent.

### 3.1.2. Travel restrictions

During SARS some governments forced travel restrictions, and even simple travel advisories decreased the number of voluntary travelers to SARS infected communities (Bell, 2004). This suggests that travel patterns will change in the case of flu, so it is interesting to further consider the potential effect of travel restrictions. We varied the number of travelers between the cities from our baseline number of 12 daily travelers to between 1 and 120 daily travelers. Our results are summarized in Graph 3. As the number of travelers increases the infection becomes more likely to reach the adjacent community earlier. The startling finding is that even with one daily highly-active traveler between the two communities the disease still spreads to the adjacent community with an incredibly high probability. This indicates that travel restrictions unless 100% effective will fail to stop infection spread. During the outbreak the number of sick grows exponentially, while the restriction only decreases travel by a fixed factor, as a result incomplete travel controls only delay the spread, by one or two days until the exponentially growing number of sick becomes high enough.



Graph 2. Probability of healthy travelers to a neighboring community on day  $t$ .



Graph 3. Histogram for the first day of infection initiation in the neighboring communities.

In order to stop the disease from moving into a neighboring city all travel must be stopped and the intervention must be initiated early on ( $\sim$ Day 5) and sustained beyond the peak of the epidemic ( $\sim$ Day 15) until the threat of the transition is small (Graph 2). Since travel restrictions need to last during the peak of the epidemic, the more virulent strains of the virus, which flame out faster, will require earlier, but shorter travel restrictions. Travel restrictions are more burdensome when used in combination with other interventions that spread out the virus over a longer period. Lastly, once a travel restriction fails and an infected individual enters a fully susceptible town, the travel restriction becomes totally useless because it does not change the dynamics of the disease within the newly infected town. Overall, travel restrictions are expensive, almost impossible to implement and are often ineffective.

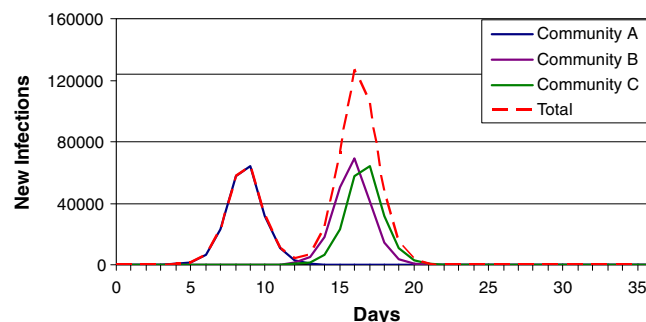
### 3.1.3. Three communities model

In a fully interconnected three community model with one initially infected community and two neighboring susceptible communities, the disease spreads almost concurrently to all of its adjacent communities (Graph 4). In the scenario where susceptible cities are connected to multiple sources of infection, the community experiencing a more severe outbreak will dominate the infecting of new cities. Given the highly connected nature of our society, unless preventative measures are put in place, the virus will spread very rapidly attacking many cities in a very short time. This could be a catastrophe for emergency systems that would face the equivalent to 50 Hurricane Katrinas hitting the United States all at once.

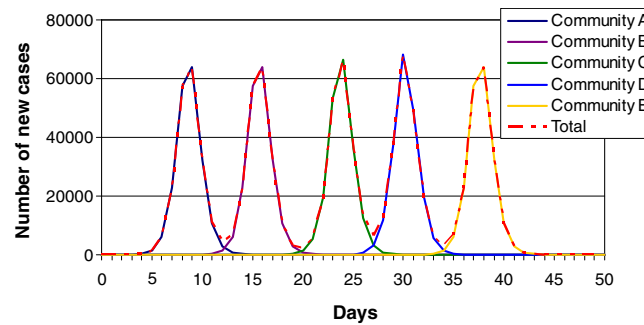
### 3.2. Chain community model

Next we address how the infection spreads to an indirectly connected community over a longer period of time. We create a chain model where the population consists of five communities labeled A through E and all travel is restricted between “adjacent” communities. (i.e., A residents can only visit B, B residents can only visit A or C, etc.). As seen in Graph 5, in our base case, once the infection enters a new community the scenario is repeated. This stylized model allows us to study the spatial disease propagation through a set of towns along the river, interstate or trade route. We avoid creating complicated community connection schematics that would be area specific, but detailed geographically tailored models exist (Ford et al., 2006, Colizza et al., 2007).

In addition to insight on infection spread on a larger scale, we consider the effectiveness and timing of interventions impacting several communities over time. As the government and public learn more about the disease, they will apply the lessons learned in the early infected communities to control and alter the course of the epidemic. A model should incorporate these response and control strategies in order to assess the expected damage of the pandemic. This provides a direct



Graph 4. Infection will spread concurrently to all neighboring communities.



Graph 5. Typical infection spread in a chain of five communities with no interventions.

segway into the next section of this paper: interventions and behavior changes and their effects in slowing down the spread of infection.

#### 4. Non-pharmaceutical interventions

The range of possible disease management strategies can be separated into medical responses: vaccines, anti-virals, and non-pharmaceutical interventions (NPIs): closures, social distancing, self-isolation, masks, etc. Some people have a fatalistic view that nothing short of a vaccine will stop the flu once it becomes easily transmissible and all other efforts will only slightly slow down the virus. Unfortunately no country in the world will have sufficient vaccine stockpiles, and antiviral effectiveness and usage are controversial. There is currently a dearth of strong evidence concerning the efficacy of social containment strategies in decreasing the cumulative burden of infection, which is particularly troublesome given that many of these interventions will carry significant economic, social, ethical, and logistical consequences. The World Health Organization (WHO) recommends non-pharmaceutical public health interventions as a means of containing the infection, delaying its spread and otherwise reducing the impact of the disease (WHO, 2004). Our results indicate that these behavior altering strategies could be more effective than expected. In this section we describe which non-medical policies and behavior changes have the potential to stop the epidemic.<sup>3</sup>

##### 4.1. Historical accounts

It is unlikely that society will implement measures from 1918–1919 making it “unlawful to cough and sneeze” punishing violators with up to a year in jail (Hudson, 1999). Making it a crime to shake hands and throwing people in jail for not wearing masks is an extreme that would only perpetuate panic and protest, but it is clear that even without forceful implementation people will try to decrease their likelihoods of getting ill by improving hygiene related behaviors. Most people will not maintain their daily routines if they discover that there is a deadly disease attacking within their city, state, country or world. Based on the information portrayed in the media, individuals are likely to both limit their daily contacts and decrease the closeness of the remaining contacts. History has provided us with multiple examples of people responding to news of a disease by altering their daily behavior.

Recent statistical studies of the 1918 influenza pandemic in US cities have supported the hypothesis that early implementation of multiple non-pharmaceutical interventions could reduce transmission rates by 30–50% and lower the peak death rates by about 50% (Bootsma and Ferguson, 2007, Hatchett et al., 2007). The timing and force of these interventions have been attributed as one of the main reasons for the variation of different cities’ experiences (Bootsma and Ferguson, 2007). The array of outcomes ranges from the Philadelphia one hump epidemic curve lasting a month and a half with a peak excess death rate of over 250/100,000 population, to the St. Louis two wave four month experience with a peak excess death rate of less than 75/100,000 population (Hatchett et al., 2007). The findings of these studies suggest that these interventions within cities helped save lives during the 1918–1919 pandemic, and may help save future lives.

A much more recent example of the social behavior changes that occurred during SARS supports the importance of incorporating non-pharmaceutical interventions into our model. Surveys indicate that during the SARS outbreak in Hong Kong 78% of the population covered their mouths while sneezing or coughing, 76% of individuals wore masks, 65% washed their hands after contact with possibly contaminated objects (Lo Janice et al., 2005). Economic factor studies in

<sup>3</sup> We are able to include vaccination in our model. The results of that work can be found in the following working paper at <http://esd.mit.edu/WPS/2007/esd-wp-2007-28.pdf>. (Nigmatulina, K.R., Larson, R.C., 2008. Stopping pandemic flu: government and community interventions in a multi-community model.)



Hong Kong, Singapore and Toronto indicate that there was a sharp drop in interactive social activities as restaurants and entertainment centers suffered sharp drops in clientele (Fan, 2003). Specifically in Hong Kong, tourism was crippled in March when the WHO issued a rare warning for travelers to avoid Hong Kong and the Guangdong Province. As a result of weakening demand airlines slashed more than a third of flights and hotels reportedly were up to 90% empty (Wiseman, 2003). In Singapore sales were down about 30% as people avoided stores and malls, and some stores suffered up to 75% declines in sales (Wiseman, 2003). It is clear that voluntary activities like tourism were strongly affected by fear of the disease.

In a more Western city of Toronto, during the SARS outbreak there was a reported drop of up to 71.5% in revenue per available hotel room for downtown Toronto. This translates into hotel occupancy rates in the range of 30–40%, instead of the seasonal 70% average (Rosszell, 2003). At least five major citywide conventions were called off, contributing a loss of over 20,000 attendees, and this does not include the vast amount of individual-hotel convention businesses that were also cancelled (Rosszell, 2003). The long list of voluntary behavior changes in Toronto due to SARS includes cancellation of over 800 bus tours, music concerts, corporate travel, and school field trips (Rosszell, 2003). All these examples are strong evidence that people will not maintain their daily actions. While we have not found any reports correlating these behavior reactions to media reports on a daily basis, we know that the effect of these “soft” and self-imposed interventions was significant (Tang and Wong, 2003). There are significant gaps in our knowledge of these behavior changes, but overlooking these behavior changes would be indefensible.

#### 4.2. Modeling the human concern factor

It is clear that people will react to the news of infection spread and alter their daily routines depending on the severity of the news. There are several social behavior models that predict that people will alter their behavior given knowledge of a deadly infection. Coping responses affect human functions to moderate and decrease the negative impacts and stressors in life's circumstances (Pearlin et al., 1981). Protection motivation theory, the transactional model of stress and coping, the health belief model (HBM) and behavior intention model (BIM) all indicate that individuals will attempt to assess their perceived risk or attitude towards the threat based on factors like threat severity and their vulnerability (TCW, 2004). Combining threat assessment with perceived response efficacy and level of confidence in one's ability to react appropriately, individuals determine their intended and actual behavior (TCW, 2004). A comparative study of the HBM and BIM in predicting human intentions regarding the swine flu vaccination program undertaken in October 1976 found that while the BIM is a better predictor, practitioners can apply the concepts of either model to the decision making process (Oliver and Berger, 1979). Motivated by social science risk perception and health behavior models, a survey study of five European and three Asian regions revealed that in a hypothetical pandemic precautionary measures would be taken across all regions, the measures included avoidance of public transportation, entertainment venues and partial isolation within the home (Sadique et al., 2007). If vaccines and anti-virals will be unavailable, the concern level will increase throughout the epidemic and individuals' coping options will be to limit their daily contacts and/or decrease the probability of transmission given contact. Before delving into these cases we explain our approach in evaluating the overall perceived level of community concern.

It is difficult to predict which kind of information people will use to assess their “perceived threat”. Logical choices for evaluating susceptibility will be the virus' proximity to home and its virulence, while mortality and morbidity rates are likely to determine perceived severity. Since we do not specify the death rate for the disease the number of infected individuals is the best gauge that reflects both community members' vulnerability to the disease and the severity of the threat. We apply the concepts of the various behavior models and use this factor to gauge human reaction. While our approach may seem primitive, there has been little progress in the field of quantitative health behavior modeling (Weinstein and Rothman, 2005). We suggest one method for incorporating behavior changes into our model and it is supported by Sadique's questionnaire study results, but further research is required in this area (Sadique et al., 2007).

In order to incorporate behavior change into our model we use  $\pi_X(t)$  as a feedback parameter that indicates the “concern level” within Community  $X$  on day  $t$ . If  $\pi_X(t) = 1$  then there is no anxiety or behavior change within the community, but for  $\pi_X(t) = 0$  the community practically shuts down. We describe three possible data sets that the population could use to gauge their risk levels, to define their  $\pi_X(t)$  and consequently alter their behavior.

1. The first communities that experience the virus will not be able to use the lessons learned by their neighbors. Early on the only information people will have will be the experience of their own community. People may use the number of yesterday's new infections ignoring everything that happened before yesterday. We quantify this memoryless approach of evaluating the risk factor as  $\pi_X^1(t, C_1)$

$$\pi_X^1(t, C_1) = \left( 1 - \frac{\text{Number of infected people in Community } X \text{ from day } t-1}{\text{The total population in Community } X} \right)^{C_1}.$$

$C_1$  an input that represents the importance of yesterday's information to the people. For  $C_1 = 1$  the number of infected individuals is linearly correlated to the risk level. As  $C_1$  grows, the relevance and impact of yesterday's news grows polynomially.<sup>4</sup>

2. The media is likely to present the cumulative number of infections within the community, this is another possible data set that people may use to estimate their risk levels. The related concern parameter is  $\pi_X^2(t)$

$$\pi_X^2(t, C_2) = \left(1 - \frac{\text{Number of infecteds in Community } X \text{ up to and including day } t - 1}{\text{The total population in Community } X}\right)^{C_2}.$$

$C_2$  is another input which represents the strength of impact of this cumulative information. We acknowledge that  $C_1$  will have a smaller impact than  $C_2$  of the exact same value.<sup>5</sup>

3. It is also clear that if a city's adjacent communities all get infected the level of concern within the city will be heightened to reflect the suffering of its neighbors. This presents us with another factor in evaluating the behavior change feedback parameter,  $\pi_X^3(t)$

$$\pi_X^3(t, C_3) = \left(1 - \frac{\text{Number of infecteds in all Communities up to and including day } t - 1}{\text{The total population in all Communities that have been infected}}\right)^{C_3}.$$

Again  $C_3$  is an input representing the impact of this information. Notice the denominator is the population of only the infected communities, so this reflects a human informational bias that focuses on only the infected communities.

In reality each individual is likely to change her behavior using a combination of all three described approaches. In our model we can uniformly alter the actions of people within each group using  $\pi_X(t, C_1, C_2, C_3) = \pi_X^1(t, C_1) * \pi_X^2(t, C_2) * \pi_X^3(t, C_3)$  as the feedback parameter for behavior change. The two parameters that will incorporate  $\pi_X(t, C_1, C_2, C_3)$  to reflect changing behavior due to awareness and alarm over the infection are  $\lambda$  and  $p$ .

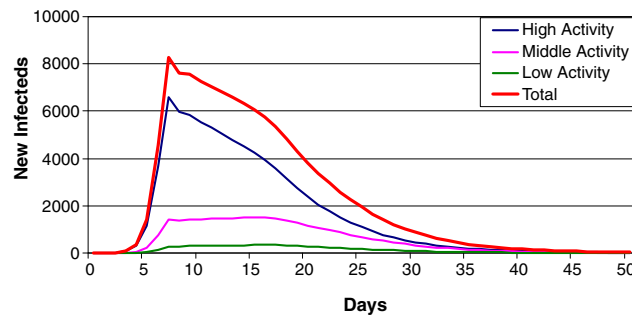
#### 4.3. Limited contact

People in all activity levels are likely to decrease the number of contacts that they have on a daily level. It is highly probable that children will be kept at home, public transportation will be avoided, entertainment activities such as shopping or going to the movies will be temporarily suspended, even the number of contacts within the office may decrease as conference calls replace face-to-face contacts (Sadique et al., 2007). All these behavior changes were observed during the SARS outbreak (Wiseman, 2003). We model behavior change by updating the average number of daily contacts,  $\lambda'$ , by multiplying it by,  $\pi_X(t, C_1, C_2, C_3)$ , the appropriate level of impact. As can be seen from Graph 6, relying on yesterday's information as the indicator for the concern level results in a lowered peak of the epidemic but a much slower decline of the disease. The cumulative number of infections is decreased but the virus maintains its presence within the community for a long period of time requiring sustained measures. However, people are likely to use more than just yesterday's information to define their behavior. If the community can "remember" the number of people who were infected prior to yesterday, then the virus declines much faster. Graph 7 illustrates the potential success of social distancing in decreasing the cumulative number of infecteds to a small fraction of the total population and in stopping the infection within a community. Refer to Graph 8 to see how the experiences of prior infected communities can benefit the communities further down the infection chain. Social distancing where the average number of daily contacts is decreased up to 80%, at the height of the danger for each activity group, is the extent of limited contact sufficient to stop the outbreak in Community B. It is clear that the most cautious communities that change their behavior prior to the infection entrance are the most successful. This voluntary public action will also decrease the probability of the infection entering the community in the first place.

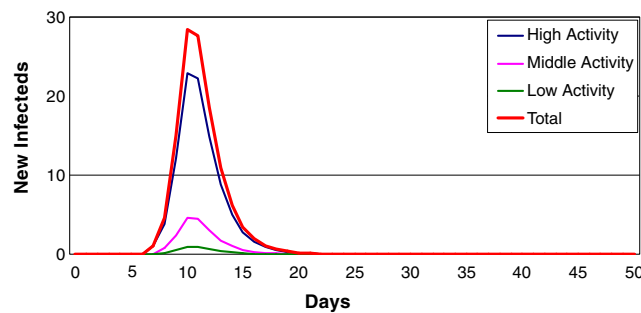
The average number of interactions is likely to decrease, but it is unlikely that the  $\lambda$ 's are going to change the same for each activity level. Highly active people will be able to decrease their number of interactions drastically, but less active people may be unable to sever their few, but vital ties to the community. For example, a politician may decide to cancel his/her campaign rally, stay at home and contact his office through telecommunication. On the other extreme, a retired handicapped grandmother whose only daily contact is with her grandson who brings her daily groceries, is not likely to change her pattern at all.

<sup>4</sup> The authors have not been able to find the application of the behavior forecasting models to predict general behavior changes in the case of pandemic flu, but we have found numerous examples of HBM used to estimate altered human interactions to reduce their risk for HIV infection. Studies in this area indicate that there may be non-linear relationships between the factors and the dependent variable, thus we allowed for this variability through the addition of the  $C$  parameters (Stiles and Kaplan, 2004).

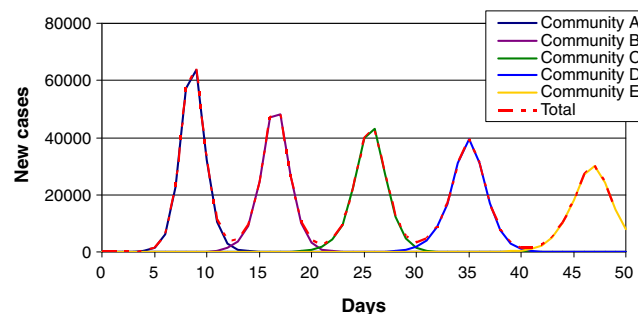
<sup>5</sup> Studies in this area indicate that there may be non-linear relationships between the factors and the dependent variable, thus we allowed for this variability through the addition of the  $C$  parameters.



Graph 6. Infection spread within a community that reacts, by proportional scaling back the average number of contacts for all its members, to previous day's news only.



Graph 7. Infection spread within a community that reacts, by social distancing, to news cumulative over all previous days across all communities.

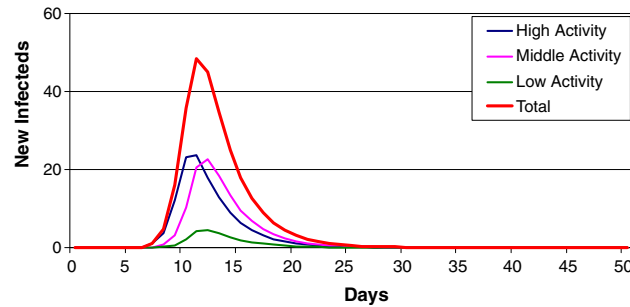


Graph 8. Infection spread in a linked chain of five communities where each implements an intermediate level social distancing based on experiences of the previous communities.

This leads us to consider the scenario where only the highly active individuals, with many voluntary contacts, limit their daily contacts. The results are presented in [Graph 9](#). Just changing the behavior of the highly active individuals has a similar impact as decreasing the behavior of the entire community. If highly active individuals decrease their number of daily contacts by about 80% during the riskiest time, then a massive communitywide outbreak could be prevented. This result has multiple policy implications. It underlines the importance of closing schools since children have a high number of non-vital daily contacts within a school setting. All individuals who act as social focal points should decrease their average number of contacts especially if this can be done without disrupting the community.

#### 4.4. Decreased probability of transmission

Reduced closeness of contact and improved hygiene are coping mechanisms that will decrease the probability of transmission given contact between an infected and susceptible individual. In order to reflect this phenomenon we update the probability of transmission given contact on a daily basis by multiplying  $p^i$  by the appropriate,  $\pi_X(t, C_1, C_2, C_3)$ , level of impact. In our model the impact of decreased susceptibility is the same as the impact of decreased contact. Since our model provides us with the expected number of infecteds, we incorporate decreased probability of transmission by integrating a



Graph 9. Infection spread within a community that reacts by social distancing only in the highly active group, to news over all previous days across all communities.

multiple of the risk factor in the exponent. As before if people start taking precautions based solely on yesterday's information they will lower the peak and extend the length of the epidemic curve (Graph 6). If the probability of transmission is dependent on all information up to and including yesterday then the length of the epidemic is shorter (Graph 7). Also, we can combine the two protective approaches and decrease the average number of contacts and limit the probability of transmission. For example, to stop the outbreak, highly active individuals need to decrease to an average of 15 daily contacts and a transmission parameter of about 5.5% (Graph 9).

#### 4.5. Implications of behavior models

Some of the concepts highlighted in the social behavior predicting models strengthen the importance of our findings. An important factor in the BIM is the perceived behavioral control – the ability to perform the behavior (TCW, 2004). If individuals believe that they can easily fulfill the necessary requirements they are much more likely to act accordingly (TCW, 2004). This implies that the relevant institutions should be prepared to implement appropriate leave-of-absence laws and help citizens maintain high levels of hygiene during the pandemic. BIM also emphasizes the importance of subjective norms – humans' actions reflect what others believe is the right thing to do (TCW, 2004). In the course of a pandemic public figures from local and federal governments could influence their constituents by explaining the importance of control measures to the public. The transaction model of stress and coping indicates that in a stressful situation individuals will demonstrate “information seeking behavior”, implying that the media must portray information in a constructive manner (TCW, 2004). Educating the public can ensure the cooperation of individuals; when people do not understand the risks they do not act (Hong and Collins, 2006). The main conclusion we draw from these behavior feedback models is that the information portrayed in the media, both about the extent of the epidemic and our ability to manage the situation, will help determine peoples' reactions and thus directly impact the course of the pandemic.

### 5. Conclusions and policy implications

“How would a nation so greatly moved and touched by the 3,000 dead of September 11<sup>th</sup> react to half a million dead? ... to 5 or 50 million dead?” ~Words of Senator (Bill Frist in thinking about pandemic influenza, 2005).

#### 5.1. Conclusions

The paradox of a pandemic is that it is a worldwide catastrophe that will be felt intensely at the local level since there is no one who will be “outside” of the pandemic to send help (Greger, 2006, Dept.Agr., 2006). Communities will have to use their own resources to cope with the pandemic. Therefore it is vital that all levels of society: families, businesses, cities, states, countries, are all prepared for the pandemic. The best plan will require the cooperation of the American people, and in order to gain the trust and understanding of 300 million people it is we must be prepared to educate the public on the important factors of the infection.

While epidemiologists sometimes refer to a lack of parameter knowledge as reason to avoid adding complexity to models, we believe that intuitive understanding of disease dynamics can only be improved by looking at lessons learned from experience, logic, and most importantly well organized models. In the end, mathematical models remain just that – models, not real life. All models use assumptions and simplifying approaches and no approach should be thought of as the only modeling strategy. Even the most established modeling approaches should not be seen as boundaries, but as starting points for future work. By moving beyond the highly used  $R_0$  parameter in our modeling work, we were able to observe the vital

importance of highly active individuals in the spread of infection. Avoiding this limiting approach we were able to include a dynamically updating component to describe reactive behavior changes into our model. As a result our study provides insights regarding the effectiveness of intervention strategies in reducing the illness and death caused by pandemic influenza and its spread in the community.

### 5.1.1. Policy implications

The bad news is that a flu pandemic is coming; the good news is that our society has the capacity to mitigate its outcome. To succeed we require careful, deliberate and thorough plans that are prepared and reviewed today, before the outbreak, and are ready to be implemented immediately at the first sign of a dangerous easily transmitting flu strain. Ethical dilemmas of forced restrictions or unequal treatment should be dealt with now, otherwise they will consume crucial time when our society should be taking action.

Travel restrictions are impossible and useless once the infection is circulating within the country. There is no easy way to regulate the travel patterns of all individuals through all transportation networks including cars, buses, trains, etc, so the restrictions will be imperfect, costly and futile. We recommend avoiding government-enforced travel restrictions, but possibly creating early travel advisories before the virus enters the country to prevent recreational and voluntary travel and potentially delay the pandemic without severe economic losses.

From our research we find while these advisories may slightly delay the spread of the flu, they will not stop it from reaching the US. Virtually every community in the US should be prepared, assuming that they will become infected. The focus of these communities' mitigation strategies must be inner-community interventions: social distancing, hygienic steps. If communities are able to decrease their maximum number of daily infected individuals they will reduce the probability of intra-community infection transmission as a byproduct of the inner-community action.<sup>6</sup> Our findings are encouraging and support the hypothesis that limited interaction will decrease the effect of the pandemic. The deeper insight of this result is that these interventions are effective because they attack the source of the problem by decreasing the exponential growth factor. Preventing exponential explosion of the number of infecteds will prevent the pandemic.

Another result of our behavioral study is that the focus must be on the group most culpable for infection spread: the highly susceptible and highly active individuals. These are the people who must be deterred from maintaining their daily actions. In addition, it is critical for all people to remember the effect of the epidemic and maintain their distance beyond the peak of the outbreak. The media should present information regarding the events over the whole history of the epidemic, remind communities about the state of their neighboring and other communities and educates individuals and empowers them to take preventative action. These informative messages will determine human behavior and that will determine the course of the pandemic.

### Note added in proof

As of March 11 2008, the number of reported cases of people infected by the H5N1 virus has climbed to 372, with 235 deaths in 14 countries ([http://www.who.int/csr/disease/avian\\_influenza/country/cases\\_table\\_20\\_08\\_03\\_11/en/index.html](http://www.who.int/csr/disease/avian_influenza/country/cases_table_20_08_03_11/en/index.html)).

### Acknowledgements

This work was supported by the Sloan Foundation of New York and by IBM. The authors are grateful for that support and for the helpful comments of MIT colleague Dr. Stan Finkelstein.

### References

- Becker, N.G., 1974. On parametric estimation for mortal branching processes. *Biometrika* 61 (2), 393–399.
- Becker, N.G., 1989. Analysis of infectious disease data. Monographs on Statistics and Applied Probability. Chapman and Hall.
- Bell, D.M., 2004. World Health Organization working group on prevention of international and community transmission of SARS. Public health interventions and SARS spread, 2003. *Emerging Infectious Diseases* (November). <<http://www.cdc.gov/ncidod/EID/vol10no11/04-0729.htm>>.
- Bootsma, M.C.J., Ferguson, N.M., 2007. The effect of public health measures on the 1918 influenza pandemic in U.S. cities. *Proceedings of the National Academy of Sciences of the United States* (April 6). <<http://www.pnas.org/cgi/content/abstract/0611071104v1>>.
- Carr-Brown, J., Britain prepares for bird flu death toll of thousands. *The Sunday Times*. August 7, 2005. <<http://timesonline.co.uk/article/0,2087-1724318,00.html>>.
- Centers for Disease Control and Prevention, 2005. Avian influenza infections in humans (May 24). <<http://www.cdc.gov/flu/avian/gen-info/avian-flu-humans.htm>>.
- Christley, R.M. et al., 2005. Infection in social networks: Using network analysis to identify high-risk individuals. *American Journal of Epidemiology* (September) <<http://aje.oxfordjournals.org/cgi/content/abstract/162/10/1024>>.

<sup>6</sup> The reverse is not true. Travel restrictions have no impact on inner-community infection dynamics.



- Colizza, V., Barrat, A., Barthélemy, M., Vallerons, A.J., Vespignani, A., 2007. Modeling the worldwide spread of pandemic influenza: Baseline case and containment interventions. *PLoS Medicine* 4 (1), 95–110 <<http://medicine.plosjournals.org/archive/1549-1676/4/1/pdf/10.1371journal.pmed.0040013-L.pdf>>.
- Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J., 1990. On the definition and the computation of the basic reproduction ratio  $R_0$  in models for infectious diseases in heterogeneous populations. *Journal of Mathematical Biology* 28, 365–382.
- Dietz, K., 1975. Transmission and Control in Arbovirus Diseases. In: Ludwig, D., Cooke, K.L. (Eds.), *Epidemiology*. Society for Industrial and Applied Mathematics, Philadelphia, pp. 104–121 <[http://igitur-archive.library.uu.nl/vet/2006-0321-200227/heesterbeek\\_02\\_daniel\\_bernoulli's.pdf](http://igitur-archive.library.uu.nl/vet/2006-0321-200227/heesterbeek_02_daniel_bernoulli's.pdf)>.
- Dietz, K., Heesterbeek, J.A.P., 2002. Daniel Bernoulli's epidemiological model revisited. *Mathematical Biosciences* 180, 1–21.
- Enserink, M., 2004. Bird flu infected 1,000, Dutch researchers say. *Science* 306, 590.
- Eubank, S., Guclu, H., Kumar, A.V.S., Marathe, M.V., Srivasan, A., Toroczkai, Z., Wang, N., 2004. Modeling disease outbreaks in realistic urban social networks. *Nature* 429 (May 13), 180–184 <<http://cnls.lanl.gov/~toro/nat02541.pdf>>.
- Fan, Emma Xiaoqin, 2003. SARS: Economic impacts and implications. ERD policy brief, Economics and Research Department. Asian Development Bank (May). <[http://www.adb.org/Documents/EDRC/Policy\\_Briefs/PB015.pdf](http://www.adb.org/Documents/EDRC/Policy_Briefs/PB015.pdf)>.
- Ferguson, N.M., Mallett, S., Jackson, H., Roberts, N., Ward, P., 2003. A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals. *Journal of Antimicrobial Chemotherapy* 51 (May), 977–990.
- Ford, Alexander Daniel, Kaufman, James H., Iris, Eiron, 2006. An extensible spatial and temporal epidemiological modelling system. *International Journal of Health Geographics* 5, 4 <<http://www.ij-healthgeographics.com/content/5/1/4>>.
- Frist, B. 2005. Manhattan project for the 21st century. Harvard Medical School Health Care Policy Seidman Lecture (June 1). <<http://frist.senate.gov/files/060105manhattan.pdf>>.
- Fu, Y.-C., 2005. Measuring personal networks with daily contacts: A single-item survey question and the contact diary. *Soc. Networks* 27, 169–186.
- Fu, Y.-C., 2007. Contact diaries: Building archives of actual and comprehensive personal networks. *Field Methods* 19 (2), 194–217.
- Gerberding, J.L., 2005. Current status of avian influenza and pandemic threat. In: Institute of Medicine of the National Academies, John R. La Montagne Memorial Symposium on Pandemic Influenza Research: Meeting Proceedings, National Academies Press, Washington, DC, p. 12.
- Germann, T.C., Kadau, K., Longini Jr., I.M., Macken, C., 2006. Mitigation strategies for pandemic influenza in the United States. *Proceedings of the National Academy of Science of the United States* 103, 5935.
- Greger, Michael, 2006. Coming soon to a theater near you. Birdflu a virus of our own hatching <<http://birdflubook.com/g.php?id=5>>.
- Hatchett, R.J., Mecher, C.E., Lipsitch, M., 2007. Public health interventions and epidemic intensity during the 1918 influenza pandemic. In: *Proceedings of the National Academy of Sciences of the United States* (April 6). <<http://www.pnas.org/cgi/content/abstract/0610941104v1>>.
- Herda, P.S., 1995. The 1918 influenza pandemic in Fiji, Tonga, and the Samoas. In: Bryder, L., Dow, D.A. (Eds.), *New Countries and Old Medicine: Proceedings of an International Conference on the History of Medicine and Health Auckland*. Pyramid Press, New Zealand, pp. 46–53.
- Hethcote, H.W., 2000. The mathematics of infectious diseases. *Society for Industrial and Applied Mathematics. SIAM Review* 42 (4), 599–653 <<http://www.siam.org/journals/sirev/42-4/37190.html>>.
- Holmberg, S.D., Layton, C.M., Ghneim, G.S., Wagener, D.K., 2006. State plans for containment of pandemic influenza. *Emerging Infectious Diseases* <<http://www.cdc.gov/ncidod/EID/vol12no09/06-0369.htm>>.
- Hong, S., Collins, A., 2006. Societal responses to familiar versus unfamiliar risk: Comparisons of influenza and SARS in Korea. *Risk Analysis* 26 (5), 1247–1257 <<http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1539-6924.2006.00812.x>>.
- Hudson, C., 1999. Something in the air. *Daily Mail* (August 21), 30–31.
- Hyman, J.M., Li, J., 2000. An intuitive formulation for the reproductive number for the spread of disease in heterogeneous populations. *Mathematical Biosciences*, 65–86 <<http://math.lanl.gov/~mac/papers/bio/HL00.pdf>>.
- Implementation Plan for the National Strategy for Pandemic Influenza (IPNSPI), 2006. Institutions: Protecting personnel and ensuring continuity of operations. Homeland Security Council, May (Chapter 9). <[https://www.whitehouse.gov/homeland/nspi\\_implementation\\_chap09.pdf](https://www.whitehouse.gov/homeland/nspi_implementation_chap09.pdf)>.
- Karesh, W., Cook, R.A., 2005. The human–animal link. *Foreign Affairs* 84 (4), 38–50 <<http://foreignaffairs.org/20050701faessa...link.html?mode=print>>.
- Knox, N., 2005. Europe braces for avian flu. *USA Today* (October 9). <[http://www.usatoday.com/news/health/2005..rope-avian-flu\\_x.htm](http://www.usatoday.com/news/health/2005..rope-avian-flu_x.htm)>.
- Larson, R.C., 2007. Simple models of influenza progression within a heterogeneous population. *Operations Research* 55 (3), 399–412.
- Lo Janice, Y.C., Thomas, H.F., Tsang Yiu-Hong, Leung, et al., 2005. Respiratory Infections during SARS outbreak, Hong Kong, 2003. *Emerging Infectious Diseases* 11 (11), 1738–1741.
- Longini Jr., I.M., Nizam, A., Xu, S., Ungchusak, K., Hanshaworakul, W., Cummings, D.A.T., Halloran, M.E., 2005. Containing pandemic influenza at the source. *Science* 309 (August 12), 1083–1087.
- MacDonald, G., 1952. The analysis of equilibrium in malaria. *Tropical Disease Bulletin* 49, 813–829.
- McKibbin, Warwick, 2006. Global macroeconomic consequences of pandemic influenza. Lowy Institute for International Policy, Sydney (February). <<http://www.lowyinstitute.org/Publication.asp?pid=345>>.
- Neergaard, L., 2005. Is it Time to Vaccinate More Kids to Stop Flu's Spread? *Canadian Press* <<http://www.canada.com/health/story.html?id=9e81fb26-f98c-4109-98ad-8703405f3370>>.
- Oliver, Riachrd, Berger, Philip, 1979. A path analysis of preventive health care decision models. *Journal of Consumer Research* 6 (September), 113–121.
- Pearlin, L.I., Menaghan, E.G., Lieberman, M.A., Mullan, J.T., 1981. The stress process. *Journal of Health and Social Behavior* 22, 337–356.
- Roszell, Monique, 2003. SARS and its impact on tourism in Toronto. *Canadian Lodging Outlook and HVS International*, Toronto (May) <[http://www.hotelonline.com/News/PR2003\\_2nd/May03\\_CanadianReview.html](http://www.hotelonline.com/News/PR2003_2nd/May03_CanadianReview.html)>.
- Sadique, M.Z. et al., 2007. Precautionary behavior in response to perceived threat of pandemic influenza. *Emerging Infectious Diseases* (September) <<http://www.cdc.gov/EID/content/13/9/1307.htm>>.
- Stiles, B., Kaplan, H., 2004. Factors influencing change behavior: Risk reduction for HIV infection. *Social Behavior and Personality* <[http://findarticles.com/p/articles/mi\\_qa3852/is\\_200401/ai\\_n9437692](http://findarticles.com/p/articles/mi_qa3852/is_200401/ai_n9437692)>.
- Tang, Catherine, Wong, Chi-yan, 2003. An outbreak of the severe acute respiratory syndrome: Predictors of health behaviors and effect of community prevention measures in Hong Kong, China. *American Journal of Public Health*. 93 (11), 1887–1888 <<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1448068>>.
- TCW, 2004. Health Communication. University of Twente, Netherlands (September).
- Underwood, Anne, 2005. Resurrecting a Killer Fly: A scientist explain why he re-created the lethal virus that killed millions in 1918 and what it can teach us about today's flu. *Newsweek* (October 7).

- U.S. Department of Agriculture National Agricultural Statistics Service, 2006. Poultry slaughter-2005 annual summary (February). <<http://usda.mannlib.cornell.edu/usda/cur..lauSu-02-28-2006.pdf>>.
- Wallinga, Jacco, Teunis, Peter, Kretzschmar, Mirjam, 2006. Using data on social contacts to estimate age-specific transmission parameters for respiratory spread infectious agents. *American Journal of Epidemiology* 164 (10), 936–944 <<http://aje.oxfordjournals.org/cgi/content/abstract/164/10/936>>. Advance Access published September 12.
- Weaver, J., 2005. What can nervous Americans do about bird flu? MSNBC 18 (October) <<http://www.msnbc.msn.com/id/9727728>>.
- Weinstein, N.D., Rothman, A.J., 2005. Commentary: Revitalizing research on health behavior theories. *Health Education Research* 20 (3), 294–297 <<http://her.oxfordjournals.org/cgi/content/full/20/3/294>>.
- World Health Organization, 1972. Smallpox: Yugoslavia. *Weekly Epidemiology Record* 47, 161–162.
- World Health Organization, 2004. WHO consultation on priority public health interventions before and during an influenza pandemic. Department of Communicable Disease Surveillance and Response, Geneva, Switzerland (16–18th March) <[http://www.who.int/csr/disease/avian\\_influenza/final.pdf](http://www.who.int/csr/disease/avian_influenza/final.pdf)>.
- World Health Organization (WHO), 2008. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO (12th March) <[http://www.who.int/csr/disease/avian\\_influenza/country/cases\\_table\\_2008\\_03\\_11/en/index.html](http://www.who.int/csr/disease/avian_influenza/country/cases_table_2008_03_11/en/index.html)>.
- Wiseman, Paul, 2003. SARS in Hong Kong behavior changes: Panic over illness has bigger impact than SARS itself. *USA Today* 14 (1) <[http://www.usatoday.com/money/economy/2003-04-13-sars-asia\\_x.htm](http://www.usatoday.com/money/economy/2003-04-13-sars-asia_x.htm)>.
- Zeng, Xiaoming, Wagner, Michael, 2002. Modeling the effects of epidemics on routinely collected data. *Journal of the American Medical Informatics Association* 9 (6) <[http://www.jamia.org/cgi/content/abstract/9/6\\_suppl\\_1/S17](http://www.jamia.org/cgi/content/abstract/9/6_suppl_1/S17)>.